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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/600,134	06/20/2003	Neil H. Bander	10448-185002	8778

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EXAMINER	
HUMPHREY, DAVID HAROLD	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 11/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/600,134	BANDER ET AL.	
	Examiner	Art Unit	
	David Humphrey	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-26 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-26 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 20 June 2003 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 8/02/04;12/27/04 .
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-26 are pending.

2. Claims 1-26 are examined on the merits.

Specification

3. The disclosure is objected to because of the following informalities: Applicant is advised that the address for the ATCC has recently changed, and that the new address should appear in the specification. The new address is:

American Type Culture Collection

10801 University Boulevard

Manassas, VA 20110-2209

Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. The claims 4, 5, and 6 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description.

1. It is unclear if a cell line which produces an antibody having the exact chemical identity of E99, J415, J533, and J591 is known and publicly available, or can be reproducibly isolated without undue experimentation. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

2. For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species, E99, J415, J533, and J591. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph; see 37 C.F.R. 1.801-1.809.

Applicant's referral to the deposit of hybridomas E99, J415, J533, and J591 as ATCC Accession Numbers HB-12101, HB-12109, HB-12127, and HB-12126,

respectively, on page 13 of the specification is an insufficient assurance that the required deposit has been made and all the conditions of 37 CFR 1.801-1.809 met.

If the deposit is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposited material will be irrevocably removed upon the grant of a patent on this application. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit is not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If a deposit is made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the biological material described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3, 4, 5, 6, and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 3 is vague and indefinite for the recitation of "antigen-binding portion thereof is a monoclonal antibody". It is unclear how a portion of an antibody can still be referred to as a monoclonal antibody. Monoclonal antibodies contain two smaller proteins (light chains) and two larger proteins (heavy chains). Each of the four chains of the antibody contains a constant region and a variable region. Since the antigen-binding portion does not contain all these components, it is unclear how the antigen-binding portion could be a monoclonal antibody. As written, the metes and bounds of the claims cannot be determined.

b. Claim 23 is vague and indefinite for the recitation "high index of suspicion of cancer". It is not clear what factors contribute to the index of suspicion. Possible factors could be age, family history, as well as the results of diagnostic laboratory tests such as the presence of prostate specific antigen (PSA) in the urine. As written, the metes and bounds of the claim cannot be determined.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

8. Claims 1-15, 25, and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Bander (WO 98/03873, International Publication Date January 28, 1998).

The claims recite a method for isolating viable cancerous epithelial cells in a solution, the method comprising providing a monoclonal antibody which binds to an extracellular domain of prostate specific membrane antigen (PSMA) and isolating cells by virtue of binding to the antibody. The claims encompass any method involving contacting a solution of viable epithelial cells with an anti-PSMA antibody and allowing the antibody to bind. Therefore, the claimed method encompasses the use of labeled anti-PSMA antibodies binding to epithelial for immunofluorescence and flow cytometry for example.

Bander teaches a method for detecting viable cancerous epithelial cells or vascular endothelial cells in a solution by using monoclonal antibodies that bind to an extracellular domain of PSMA, see Abstract. The method involves contacting the cells with an antibody, such as E99, J415, J533, and J591, bound to a label effective to permit detection of the cells expressing PSMA, see page 17 line 34 through page 18, line 17 and page 24 Table 1. Bander teaches that the antibodies listed in Table 1 can be used alone or as a component of a mixture with other antibodies or biological agents, see page 24, lines 23-28. Bander further teaches that the contact step can be carried

out in a sample of serum, urine or other body fluid to detect the presence of PSMA in the body fluid, see page 19, lines 1-11. Bander also teaches that the methods of the present invention can be used to detect cancerous prostate epithelial cells as well as renal, urothelial, colon, rectal, lung, breast, and metastatic adenocarcinoma of the liver, see page 20, line 35 through page 21, line 8. Bander teaches the method involving culturing a prostate cancer model cell line, LNCaP, see page 36, lines 22-26. Bander also teaches the use of antigen binding portions of antibodies such as Fab fragments, $F(ab')_2$ fragments, and F_v fragments, see page 23, lines 25-31.

While the recitation of intended use for the instant application (isolation of viable epithelial cells) is different from that of Bander (detection of viable epithelial cells), the method steps of the instant application are anticipated by the teachings of Bander. Therefore, the intended use is given no patentable weight.

9. Claims 1-5, 7-13, 25 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Liu et al. (Cancer Res. 57: 3629-3624 (1997); cited as reference AY on Applicant's IDS submitted on August 2, 2004) as evidenced by Kooistra et al. (Urology Research 25, supplement 2: S97-105 (1997)).

The claims recite a method for isolating viable cancerous epithelial cells or vascular endothelial cells in a solution by providing a monoclonal antibody (E99, J415, J533, and J591) that binds to an extracellular domain of prostate specific membrane antigen (PSMA) and isolating the epithelial or endothelial cells by virtue of binding to the antibody. Claim 26 provides the further limitation that the vascular endothelial cells are

from a cancerous tissue selected from a group consisting of cancerous renal tissue, urothelial tissue, colon tissue, rectal tissue, lung tissue, breast cancer tissue, and liver metastatic adenocarcinoma.

Liu et al. teach a method of isolating viable cancerous epithelial cells or vascular endothelial cells in a solution by contacting the cells with a monoclonal antibody (E99, J415, J533, or J591) that binds to an extracellular domain of PSMA, see Abstract and page 3631, right column. Liu et al teach that the monoclonal antibodies bind to viable LNCaP cells in vitro and show strong immunohistochemical reactivity to tissue sections of prostate epithelia, including prostate cancer, see Abstract, lines 9-12. Liu et al. further teach that the anti-PSMA antibodies are strongly reactive with vascular endothelium of a wide variety of carcinomas including lung, breast, renal, urothelial, colon, and adenocarcinoma to the liver, see page 3629, Abstract; page 3629, IF Assay; and page 3632, left column, lines 10-14. As evidenced from Kooistra et al., Kooiestra teach that LNCaP is a prostatic tumor epithelial cell line, see Abstract, lines 2-4. Therefore, LNCaP cells are prostate tumor epithelial cells.

This rejection cites two references. However, the second reference (Kooiestra et al.), is cited as it provides evidence of the inherent characteristics of the LNCaP cell line which are not explicitly disclosed in Liu et al., specifically that LNCaP are prostatic tumor epithelial cells (MPEP 2131.01).

10. Claims 1-21, and 24 are rejected under 35 U.S.C. 102(e) as being anticipated by Murphy et al. (U.S. Patent 6,383,759, effective filing date May 4, 1998, patented May 7,

2002) as evidenced by Kooistra et al. (Urology Research 25, supplement 2: S97-105 (1997)).

Claim 1-21, and 24 recite a method for isolating viable epithelial cells in a solution, the method comprising providing an antibody or antigen binding portion which binds to an extracellular domain of prostate specific membrane antigen and isolating the cells by virtue of binding to the antibody. The claims further recite monoclonal antibodies E99, J415, J533, and J591 and their corresponding ATCC Accession Numbers HB-12011, HB-12109, HB-12127, and HB-12126. The epithelial cells are selected from the group of normal epithelial cells, benign hyperplastic epithelial cells, and cancerous epithelial cells. The claims further recite the limitation that the solution includes a biological fluid mixed with tissue culture media obtained from a patient during therapy after undergoing a biopsy.

Murphy et al. teach a method of isolating cancer epithelial cells by contacting a biological sample with an anti-PMSA antibody, see Abstract and column 2, lines 40-44. Murphy et al. teach an anti-PMSA monoclonal antibody or antigen-binding fragments thereof (column 7, lines 23-36) and specifically the monoclonal antibodies, E99, J415, J533 and J591 with their corresponding ATCC Accession Numbers HB-12101, HB-12109, HB-12127, and HB 12126, see column 6, lines 25-31. Murphy et al. teaches normal prostate epithelial cells, benign hyperplastic prostrate epithelial cells, and cancerous prostate epithelial cells, see column 6, lines 3-7 and prostatic adenocarcinoma, column 17, lines 64-66. Murphy et al. further teach a biological fluid consisting of blood, urine, and semen (column 8, lines 49-52), obtained from a patient

(column 3, lines 39-41 and figures 2-4) repeated one or more times (column 17 line 56 through column 18, line 9) wherein the patient has undergone a biopsy (column 3, line 59-67 and figure 4). Murphy et al. teach a solution comprises a tissue culture medium, see column 12, lines 56-58. As evidenced from Kooistra et al., Kooiestra teach that LNCaP is a prostatic tumor epithelial cell line, see Abstract, lines 2-4. Therefore, LNCaP cells are prostate tumor epithelial cells.

This rejection cites two references. However, the second reference (Kooiestra et al.), is cited as it provides evidence of the inherent characteristics of the LNCaP cell line which are not explicitly disclosed in Murphy et al., specifically that LNCaP are prostatic tumor epithelial cells (MPEP 2131.01).

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

12. Claims 1-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Murphy et al. (US Patent 6,383,759, effective filing date May 4, 1998, patented May 7, 2002) as applied to claims 1-21 and 24 above, and further in view of Fleshner et al. (J. Urology 158(2): 505-509).

The recitation of claims 1-21 and 24 are cited above in section 10. Claims 22 and 23 recite a method wherein the patient providing the sample of epithelial cells has undergone a biopsy, the biopsy is negative and there is a high index of suspicion of cancer.

The teachings of Murphy et al. are described above in section 10. Murphy et al. does not teach the method wherein the patient providing the sample has a negative biopsy and a high index of suspicion of cancer. Since claim 23 is vague and indefinite as written (see section 5 above), the Examiner interprets a "high index of suspicion" as risk factors and other predictive factors commonly associated with prostate carcinoma. These deficiencies are made up for in the teachings of Fleshner et al.

Fleshner et al. teach the prevelance of and risk factors for carcinoma in patients with 1 previously negative prostate biopsy, see Abstract.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have performed the method of Murphy et al. by obtaining samples from patients who had had a negative prostate biopsy but possessed risk factors for carcinoma by the method of Fleshner.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success since Fleshner et al. teach that 39 out of 130 men (30%) of men at risk who initially had a negative biopsy, subsequently had positive biopsies, see Abstract. Fleshner et al. teach that the known multifocal nature of prostate cancer coupled with the relatively small tissue sampling that occurs with sextant prostate biopsy raises the possibility that significant carcinoma exists within the gland despite a negative biopsy results. Fleshner et al. recommend repeat biopsy in all patients who meet the criteria for a transrectal ultrasound guided biopsy and in whom the initial biopsy is negative, see Abstract.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time was invention was made, as evidenced by the references.

Double Patenting

13. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to

be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

14. Claims 1-17 and 24-26 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10, and 13-16 of U.S. Patent No. 6,653,129 (Bander et al.). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant application encompass any method for isolating epithelial cells from a solution using an anti-PSMA antibodiy which includes the magnetizable medium of the patented invention.

Claims 1-17 and 24-26 of the instant application recite a method for isolating viable epithelial cells by contacting a solution with an antibody which binds to an extracellular domain of PSMA. These claims encompass all methods that utilize an anti-PSMA antibody to isolate viable cells including FACS, antibody affinity columns, and antibodies conjugated to magnetic beads.

Claims 1-10 and 13-16 of US Patent 6,653,129 anticipate claims 1-17 and 24-26 of the instant application. US Patent 6,653,129 recites a method for isolating viable epithelial cells using an anti-PSMA antibody conjugated to magnetic beads. Therefore, Claims 1-17 and 24-26 are directed to an invention not patentably distinct since both the claimed and patented invention recite a method for isolating viable epithelial cells using the same anti-PSMA antibodies or fragments. It would be obvious to one of ordinary skill in the art to utilize any number of antibody-based methods to isolate the cells from a solution including FACS, antibody affinity columns, and magnetic beads. For that

reason, claims 1-17 and 24-26 are anticipated and made obvious by claims 1-10 and 13-16 of US Patent 6,653,129.

Conclusion

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Humphrey whose telephone number is (571) 272-5544. The examiner can normally be reached on Mon-Fri 8:30AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER

David Humphrey, Ph.D.
November 8, 2005